Fundamental Pharmacological Principles and Introduction to Systems Pharmacology

Rada Savic, PhD
Classical Pharmacology

Two primary pillars:

1. The study and quantification of drug behavior in the body comprising
   pharmacokinetics (PK: “what the body does to the drug”) and
   pharmacodynamics (PD: “what the drug does to the body”)

2. The “receptor hypothesis”, the idea that drug action is mediated through binding to specific target molecules (which are usually proteins)
Overview

- Basic PKPD Concepts
- Classification of Drug Response
- Drug – Receptor Interaction
- Assessment of Drug Effect
BASIC PKPD CONCEPTS
Why study pharmacokinetics and pharmacodynamics?

• **Aim with drug therapy**
  – Safe and efficacious drugs of good quality

• **In simple words**
  – Satisfactory effect (the desired pharmacological effect)
  **and**
  – Tolerable side-effects (undesired effects)
Why study pharmacokinetics and pharmacodynamics?

- **Relationship between**
  - Drug concentration – desired effect
  - Drug concentration – undesired effect

- **Relationships**
  - Different for each drug

- **Knowledge about those relationships used to**
  - Evaluate the safety and efficacy of a drug
  - Establish an appropriate dosage in the patients to be treated (the target population)
  - Establish the most appropriate dosage for the individual patient
Relationships of importance for drug therapy

- Drug Therapy
- Plasma Conc.
- Biomarker
- Side-effect
- Effect

Pharmacokinetics
Pharmacodynamics
Pharmacokinetics (PK)

- What the body does to the drug
- The relation between dose and drug concentration in the body
- How the drug amount/concentration in the body changes over time following a drug dose
Pharmacodynamics (PD)

- What the drug does to the body
- The relation between drug concentration and the drug effect/side-effect
- How the drug effect/side-effect changes over time following a drug dose
Example: Thrombin inhibitor

- Dose
- Plasma Conc.
- Coagulation time (Biomarker)

- Reduced thrombosis Risk (Effect)
- Increased bleeding Incidence (Side-effect)
CLASSIFICATION OF RESPONSE
Definitions

Biomarker/Surrogate/Clinical end-point

• **Biomarker**
  Characteristic that is measured and evaluated as an indicator of normal biological, pathogenic or pharmacological processes.

• **Clinical endpoint**
  Characteristic or variable that measures how a patient feels, functions or survives.

• **Surrogate endpoint**
  Biomarker intended to substitute for a clinical endpoint. Known to be statistically associated with and believed to be pathophysiologically related to a clinical end-point, in literal sense; replace ultimate clinical end-point.
Surrogate endpoint examples

- Blood pressure (stroke), cholesterol (stroke)
- Intra ocular pressure (glaucoma)
- Viral load (HIV-1 RNA plasma levels) as surrogate for risk of progression to AIDS
- Testosterone levels in chemical castration
## Examples of biomarkers/surrogate endpoints

<table>
<thead>
<tr>
<th>Indication/Drug</th>
<th>Biomarker/Surrogate</th>
<th>Clinical end-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Blood pressure</td>
<td>Morbidity/Mortality</td>
</tr>
<tr>
<td>CAD/lipid lowering</td>
<td>S-cholesterol</td>
<td>Mortality</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>IOP</td>
<td>Loss of vision</td>
</tr>
<tr>
<td>HIV</td>
<td>Viral load (HIV-1 RNA)</td>
<td>Progression to AIDS</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>Acid secretion, pH</td>
<td>Healing rate</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>BMD</td>
<td>Number of fractures</td>
</tr>
</tbody>
</table>
Why biomarkers/surrogate end-points?

- Diagnosis
- Early answer to likelihood of therapeutic success
- Early demonstration of dose- and conc-response relations
- Dose selection
- Reduced sample size and/or study duration
- True endpoint unduly invasive, uncomfortable and/or expensive
- Guide therapy
DRUG – RECEPTOR INTERACTION
Drug as a "magic bullet"

"Drug does not act unless bound" - Paul Ehrlich
Drug targets

From: Goodman and Gilman’s, The pharmacologic basis for therapeutics
Working definition of a receptor

"A cellular macromolecule, or an assembly of macromolecules, that is concerned directly and specifically in chemical signalling between and within cells."

International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. XXXVIII. Update on Terms and Symbols in Quantitative Pharmacology

RICHARD R. NEUBIG, MICHAEL SPEDDING, TERRY KENAKIN, AND ARTHUR CHRISTOPOULOS
Drug-targeted proteins

- Receptors
- Ion channels
- Enzymes
- Carriers
# Examples of drug targets

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Agonists</th>
<th>Antagonists</th>
<th>Enzymes</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic Ach</td>
<td>nicotine</td>
<td>tubocurarine</td>
<td>cyclo-oxygenase</td>
<td>Aspirin</td>
</tr>
<tr>
<td>β-adrenoceptor</td>
<td>noradrenaline</td>
<td>propranolol</td>
<td>Angiotensin-conv.enz.</td>
<td>captopril</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>serotonin</td>
<td>ketanserin</td>
<td>HMG-CoA reductase</td>
<td>simvastatin</td>
</tr>
<tr>
<td>Dopamine (D&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>bromocryptine</td>
<td>chlorpromazine</td>
<td>MAO-B</td>
<td>selegiline</td>
</tr>
<tr>
<td>Insulin</td>
<td>insulin</td>
<td>-</td>
<td>dihydrofolate reductase</td>
<td>methotrexate</td>
</tr>
<tr>
<td>Oestrogen</td>
<td>ethinylestradiol</td>
<td>tamoxifen</td>
<td>enzym. of blood clotting</td>
<td>heparin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ion channels</th>
<th>Blockers</th>
<th>Modulators</th>
<th>Carriers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage-gated Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>local anesthetics</td>
<td>veratridine</td>
<td>Choline carrier</td>
<td>hemicholinium</td>
</tr>
<tr>
<td>Renal tubule Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>amiloride</td>
<td>aldosterone</td>
<td>noradrenaline uptake1</td>
<td>tricyclic antidepr.</td>
</tr>
<tr>
<td>Voltage-gated Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>divalent cations</td>
<td>β-adrenoceptor agon.</td>
<td>vesic. noradrenal. uptake</td>
<td>reserpine</td>
</tr>
<tr>
<td>ATP-sensitive K&lt;sup&gt;+&lt;/sup&gt;</td>
<td>ATP</td>
<td>sulfonylureas</td>
<td>Na*/K*/2Cl&lt;sup&gt;-&lt;/sup&gt; co-transport.</td>
<td>loop diuretics</td>
</tr>
<tr>
<td>GABA-gated Cl&lt;sup&gt;-&lt;/sup&gt;</td>
<td>picrotoxin</td>
<td>benzodiazepines</td>
<td>Na*/K&lt;sup&gt;+&lt;/sup&gt; pump</td>
<td>cardiac glycosides</td>
</tr>
<tr>
<td>Glu-gated cations</td>
<td>dizocilpine</td>
<td>glycine</td>
<td>Proton pump</td>
<td>omeprazole</td>
</tr>
</tbody>
</table>

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Receptor proteins - structure

Kinase-linked receptors

G-protein coupled receptors

Ligand-gated ion-channels

tyrosine kinase

Intracellular steroid receptor

Binding

Transduction
Receptor binding of ligands

\[
[L] + [R] \xrightarrow{k_{+1}} [RL] \xrightarrow{k_{-1}} \text{effect}
\]

In equilibrium:

\[k_{+1} \cdot [L] \cdot [R] = k_{-1} \cdot [RL]\]

\[K_d = \frac{k_{-1}}{k_{+1}} = \frac{[L] \cdot [R]}{[RL]}\]

- \([L]\): Ligand concentration
- \([R]\): Unbound receptor conc.
- \([RL]\): Bound receptor conc.
- \(k_{+1}\): Rate of association
- \(k_{-1}\): Rate of dissociation
- \(K_d\): Equilibrium dissociation constant
Drug-receptor interaction

- Agonism
- Antagonism
- Allosteric (=allotopic) interaction
- Syntopic interaction
Agonism/Antagonism

- An agonist is a ligand that binds to a receptor and alters the receptor state resulting in a biological response.
- An antagonist is a ligand that reduces the action of another ligand.
- Full/Partial response.
Effect coupling

Binding energy is coupled to change cell function through, e.g.:

- G-proteins
- Protein kinase modulation
- Lipid metabolism
- Activation of transcription factors
GPCR activation

70% of drugs have their effect by interfering with GPCRs
ASSESSMENT OF DRUG EFFECT
Measured Disease Status (S)

S – Clinical measure of disease severity

\[ S(t) = \text{Baseline} + \text{Disease progression} + \text{Placebo response} + \text{Drug effect} \]

- Disease progression
- Placebo response
- Drug effects

Often difficult to separate
- Objective/Subjective measure
- Time frame
Disease progression vs. Placebo effects

**Disease progression**
Characterize and quantitate disease over time
- Non-constant baseline
- Uncontaminated by placebo or treatment response
  - Primary symptoms
  - Complications
  - Drug-induced effects (adverse events)

**Placebo effects**
“Any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated”

Placebo = “I will be pleased”
Common types of disease progression

- Spontaneous cure (e.g., Infection)
- Indefinitely progressive (e.g., Alzheimer’s)
- Burnt-out state (e.g., Parkinson’s)
Cyclic/relapsing diseases

Health Status

100%

Cyclic constant
(eg Depression, Allergies)

Cyclic progressive
(eg Multiple Sclerosis)

Time
Assessment of drug effect

S – Clinical measure of disease severity

\[ S(t) = \text{Baseline} + \text{Disease progression} + \text{Placebo response} + \text{Drug effect} \]
Pharmacodynamics

• "What the drug does to the body"

• Direct relation between plasma concentration and drug effect
  – When all processes are rapid
  – At steady state

• Time-dependent relations
  – When a rate-limiting step occurs between plasma concentration and measured effect (drug distribution, receptor binding, second-messenger formation, active metabolite formation, etc.)
Why focus on plasma concentration (C) ?

- There is a relationship between concentration at the site of action (biophase) and the drug effect/toxicity.

- Concentration in the biophase is seldom accessible for monitoring, whereas plasma is easily accessible for monitoring.

- Unless the drug acts locally, it is transported to the site of action via the blood.

- Drug is transported to the major eliminating organs via the blood.
  - For systemically acting drugs, the concentration at the site of action is a function of the plasma (blood) concentration.
The Emax model

The Emax model

\[ E = \frac{E_{\text{max}} \cdot C}{EC_{50} + C} \]
Simplifications of the Emax model

• Linear model
  - \( m = \frac{E_{\text{max}}}{EC_{50}} \)
  - when \( C \ll EC_{50} \)

• Log linear model
  - \( E \) is 20-80% of \( E_{\text{max}} \)

\[
E = m \cdot C
\]

\[
E = m \cdot \ln C + i
\]
Other related models

- Including Baseline

\[ E = \text{Baseline} + \frac{E_{\text{max}} \cdot c}{EC_{50} + c} \]

- The sigmoid \( E_{\text{max}} \) model:

\[ E = \frac{E_{\text{max}} \cdot c^\gamma}{EC_{50}^\gamma + c^\gamma} \]
Therapeutic window

Effect/Side-effect

Desired pharmacological effect

Tolerable side-effect

Concentration of DRUG in blood

Time
Key points

• Observed drug effect consists of 4 underlying processes

\[ S(t) = \text{Baseline} + \text{Disease progression} + \text{Placebo response} + \text{Drug effect} \]

• The measured drug response may be biomarker, surrogate endpoint or clinical endpoint

• The measured drug response relates to efficacy and safety

• Drug response has the time course on its own

• Relationship between concentration and effect is the key for determining optimal dose and schedule
INTRODUCTION TO
SYSTEMS PHARMACOLOGY
Background

- Workshops in NIH in 2008/2010
- Participation from academia, industry and government
- Goals:
  (i) to review the state of the art in systems biology and in pharmacology and
  (ii) to determine whether a merger of the two in the new discipline of Quantitative and Systems Pharmacology (QSP) might significantly advance the discovery, development and clinical use of therapeutic drugs
Background (II)

- it remains difficult to translate preclinical discoveries into meaningful medical progress
- very little academic research is focused on the question of how to improve the efficiency and predictability of this process
- reinvigoration of pharmacology can best be accomplished by introducing concepts, methods and investigators from
  - computational biology,
  - systems biology and
  - biological engineering,
thereby allowing modern pharmacologists to apply systems-level ideas to practical problems in drug development
Academic and Industry view on QSP

Quantitative and Systems Pharmacology

Preclinical

Systems Biology
Chemical Biology
GEMMs

Network Modeling

Target Identification

Screening
Initial hits

Chemistry
lead optimization

Animal Studies
POC
PK/PD

Clinical

Systems Pharmacology

Toxicology
PK-PD

Human
PK-PD

Dose-exposure
responses

Therapeutic
index

Economics
Safety

Phase I
Safety-PK/PD

Phase II
Dosing
POC-human

Phase III
Efficacy

Phase IV
pharmacovigilance

Cumulative Cost (out of pocket 2010 USD)

$1B

$0.5B

$0

Current Academic Focus

Current Industry Focus

GEMM: Genetically Engineered Mouse Model; POC: Proof of concept
Focus on Efficacy and Toxicity
Integrative and Multi-scale

"Horizontal Integration"

Interaction of drug with:
- Target
- Target in cells
- Cellular Networks
- Multicellular Network

"Vertical Integration"

Interaction of drug with:
- Populations
- Patients
- Animals
- Organs
- Cells
- Purified Components

Pharmacogenomics
PK/PD
Chemical Biology
Systems Biology

Goal for QSP: systematic, holistic understanding of drug action
Horizontal integration

Systems pharmacology and genome medicine: a future perspective, Aislyn D Wist, Seth I Berger and Ravi Iyengar
# Model Definitions

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Heuristic model</td>
<td>Model with no specific assignment of biochemical or physiologic representation and mechanism and typically developed by trial and error; often provides intuition</td>
</tr>
<tr>
<td>Semi-mechanistic model</td>
<td>Model that aims to represent some mechanistic aspects of a physiologic processes or measured endpoints with some heuristic features. Often used when data are available only for some model features; can be multi-scale.</td>
</tr>
<tr>
<td>Mechanistic model</td>
<td>A model that explicitly represents biomolecules and their mechanisms of interaction at a physico-chemical level. Often confined to cellular networks of relatively restricted scope but has ability to represent pharmacological mechanism of action in detail.</td>
</tr>
<tr>
<td>Network model</td>
<td>A graphical model that describes a set of interacting components in an extended network at a relatively low level of detail and is typically inferred from high-throughput omic data (interactomes are one example).</td>
</tr>
<tr>
<td>Multiscale systems pharmacology model</td>
<td>A model that links phenomena at two or more spatial and temporal scales such as drug-target interaction, signaling networks in cells, physiological processes operating at the organ and tissue level, and animal or clinical data.</td>
</tr>
</tbody>
</table>
Integration of Disciplines

- QSP should address many practical aspects and questions of drug discovery and development.
Integration of Knowledge

New literature data
New clinical data

Multiscale Modeling
Disease and therapeutic concepts

Target Identification
Chemistry
lead optimization

Screening
Initial hits
Animal Studies
POC
PK/PD

Phase I
Safety-PK/PD
Phase II
Dosing
POC-human
Phase III
Efficacy
Phase IV
pharmacovigilance

Multiscale Modeling
PK/PD-dosing concepts
Understanding Variability

A. Genome:
- mutations
- epigenetic modifications
- positional effects
- VDJ rearrangements

Environment:
- growth factors
- metabolites
- ECM
- temperature

Proteome:
- protein levels
- protein localization
- protein modification
- assembly

B. Variation affecting IC50

C. Variation affecting E_max

D. Nonuniform cell behavior

Response vs. Drug Concentration
Innovation

• A growing understanding of cellular and tissue-level networks suggests that the therapeutic and toxic effects of drugs can best be understood at a systems level.

• Biochemical networks targeted by drugs are qualitatively similar but quantitatively different in different tissues, genetic backgrounds, development stages and disease states, and the operation of these networks is profoundly impacted by patient lifestyle and history.
Innovation

• QSP is innovative in breaking decisively with a “one-gene, one-receptor, one-mechanism” approach in favor of a network-centric view that relies on mathematical models to achieve the necessary integration of data and hypotheses.
Significance

- QSP draws on existing ideas and established concepts from traditional pharmacology, physiology and target-based drug discovery and will therefore serve as a link between pharmacology/physiology and new systems-level and “omics” approaches.
Approach

• understanding of disease mechanisms and therapeutic effects that span
  – biochemistry and structural studies,
  – cell and animal-based experiments and
  – clinical studies in human patients.

• Mathematical modeling and sophisticated computation will be critical in spanning multiple spatial and temporal scales.
Systems Pharmacology Research Areas

- Characterizing quantitatively and precisely the biochemistry of drug targets, the networks in which they are embedded and the effects of small molecule and biologic drugs
- Investigating the origins of variability in drug response at the single-cell, organ and patient level that arise from differences at the level of the proteome, genome and environment
- Exploiting diverse clinical and “omic” data to create pharmacodynamic biomarkers that inform integrated, multi-scale models of drug response determinants in distinct patient populations
Systems Pharmacology Research Areas

- Developing better animal and tissue models for pre-clinical pharmacology with the aim of better target validation and fewer Phase II failures

- Reconnecting tissue physiology with chemistry to facilitate pharmacological experimentation and phenotypic screening on complex systems (cells and model organisms)

- Developing and supporting information exchanges for QSP, particularly in the area of clinical data and electronic medical records
Systems Pharmacology Research Areas

- Developing new multi-scale computational models of pharmacological mechanism that span the divide between cell-level biochemical models and organism-level PK/PD models
- Developing approaches to “failure analysis” as a means to understand why drugs fail in clinical trials and how such failure might be avoided in the future
Concepts

• Variability
• Dynamics (Time)
• Quantity
EXTRA MATERIAL
IV. HYSTERESIS & EFFECT DELAY
Relating concentration to the effect

- Composite curves demonstrate drug effect related to drug concentrations
- Looking at response vs. concentration curves for a given concentration, we may achieve variable response relative to the time after drug dosing
Hysteresis Loop

Reasons for the EFFECT DELAY

• Delay of the drug distribution
• Formation of active metabolite
• Receptor up-regulation
• Indirect response
• Slow receptor binding

Some Examples:
• Anesthesia (Thiopentone)
• Pain medicine
• Warfarin
Equilibrium delay: extensive binding in heart to Na\(^+\)K\(^+\)ATPase

Proteresis Loop

**Reasons for Proteresis:**
- Tolerance development
- Receptor desensitization
- Homeostasis
- Negative physiological feedback

**Example:**
Clockwise hysteresis loop, typical of tolerance is seen after administration of diltiazem, Boyd et al., Clin Pharmacol. Ther. (1989)